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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/515,582	02/29/2000	Roland Buelow	A-63708-5/RFT/JJD	9803

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 12/26/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/515,582	BUELOW ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 16-22* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed on Oct. 15, 2001 has been entered and assigned as Paper # 9. Claims 23-25 have been canceled, Claims 1-22 are pending and under current examination.

Priority

The original claimed priority date is granted in view of the argument that the later submitted disclosure complies with the first paragraph of 35 U.S.C. 112.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION REQUIREMENT

Claims 1-14, and 16-22 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that "nucleic acids that modulate heme oxygnease activity in said cells is specifically defined on page 25, line 22", further "page 5, lines 10-17; pp25-26, lines 22-2; pages 6, lines 14-22; page 8, line 26 to page 9, line 2; and page 7, lines 1-7"; that "the claimed invention is directed to a method and not the nucleotide itself,

therefore the examiner's reference to the claimed subject matter as a genus of nucleic acids is misplaced", that "We would remind the Examiner that claim is not directed to "modulators of HO-I, rather it is directed to a method or extending the survival of an organ transplant employing "modulators of HO-I activity in said cells".

The arguments are carefully considered but found not persuasive for the reasons of record and the following.

The Office is fully aware that the claims are directed to a method of using "modulators of HO-I" and reiterated such throughout the Office action of Paper #8. However, the method comprises contacting organ transplant with nucleic acids molecules that modulate HO-I, thus, modulators of HO-I are an essential element for practicing the invention. For those skilled in the art seeking to practice the invention, it is critical to know what are these modulators, and accordingly nucleic acids encoding such. However, the only nucleic acid disclosed in the specification is the nucleic acid encoding HO-1 and expended to its potential variants having about 80% sequence identity. No art of record nor the specification discloses other nucleic acids that modulate HO-I, therefore, it is appropriate to reject the discrepancy between the disclosure of the specification and the scope of the claims under WRITTEN DESCRIPTION section of the first paragraph of 35 USC 112 because the nucleic acid molecules that modulate HO-I are essential element in practice the instant invention, and the Revised Interim Guidelines states "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY

DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434).

The disclosure in the recited "*page 5, lines 10-17; pp25-26, lines 22-2; pages 6, lines 14-22; page 8, line 26 to page 9, line 2; and page 7, lines 1-7*" are solely related to nucleic acids encoding HO-1 and variants. The so-called "specifically defined" disclosure in page 25, line 22 recites "The above described nucleic acid molecules will function to modulate the overall"[heme oxygenase-I activity of a cell with which it is contacted]", line 22 does not contain a complete sentence, and the complete sentence is a circular teaching of the recited nucleic acid molecules, because tracing back to "above", the only clearly defined nucleic acid molecules are those found in page 11, lines 18-20, "*In one embodiment, the present invention provides nucleic acids encoding heme oxygenase-I variants. These variants fall into one or more of these classes: substitutional, insertional or deletional variants*". Furthermore, the term "modulators of HO-1" is not clearly defined in the specification, given its plain meaning, it is not limited to HO-I variants, and obvious generic to a considerable number of agents and compounds, varying in sequences, chemical structures and physical properties. Thus, the circular teaching of page 25, lines 22-23 fails to describe what the molecules are apart from HO-I and variants. Such circular teaching is an invitation to further experimentation rather than a proper disclosure of the essential elements. The skilled artisan can not envision the sequences or chemical structures of the genus of modulators for HO-1, and the molecules that claims are intend to embrace.

The Revised Interim Guidelines state "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436). The specification fails to provide an adequate description to teach the identifying characteristics and the structure-function relationship of these broad classes of molecules, and accordingly does not provide a reasonable guide for those seeking to modulate the activity of HO-1.

With regard to rejections of claim recitation "nucleic acids having HO-I activity or having at least 80% sequence identity to nucleotides 81-944 of SEQ ID NO:1 and having the biological activity of human HO-I", applicants argue that the terminology is literally used in the specification, page 6, lines 22-31, that a skilled artisan would know what nucleic acid sequences are encompassed by this phrase, and submitted Exhibits 1-3 to show that skilled artisan recognizes such a description of a protein. Applicants further argue that methods are described by which one can routinely test for HO-I activity.

The arguments have been carefully considered and found not persuasive. The question is not whether a skilled artisan knows what nucleic acid sequences are encompassed by this phrase, but which of these sequences encompassed by the phrase also have the biological activity of human HO-I. The Office action of Paper #8 cited *Encyclopedia Britannica, Rudinger, and Bowie* to indicate that certain position in the protein sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all, that "THE

SIGNIFICANCE OF PARTICULAR AMINO ACIDS AND SEQUENCES FOR DIFFERENT ASPECTS OF BIOLOGICAL ACTIVITY CANNOT BE PREDICTED *A PRIORI* BUT MUST BE DETERMINED FROM CASE TO CASE BY PAINSTAKING EXPERIMENTAL STUDY". Arguments drawn to that the skilled artisan uses sequence homology to identify new molecules and that the protein could be routinely tested do not address issues whether the Written Description is proper, rather an invitation to further experimentation.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad classes of molecules that modulate the function of HO-I. Therefore, for the reasons of record and those set forth above, only the described nucleic acids encoding HO-I (i.e. SEQ ID No:1) meet the written description provision of 35 U.S.C. §112, first paragraph.

ENABLEMENT REQUIREMENT

Claims 1-14, 16-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method extending the survival of an organ transplant in a recipient comprising contacting cells of said organ transplant with a nucleic acid encoding HO-I (SEQ ID No:1), does not reasonably provide enablement for a method extending the survival of an organ transplant in a recipient comprising contacting cells of said organ transplant with a nucleic acid has about 80% sequence identity to SEQ ID No:1, or a nucleic acid that modulates HO-I activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. As discussed in the WRITTEN DESCRIPTION section, apart from the nucleic acids encoding HO-I, the specification fails to describe the sequences and common attributes of the broad classes of nucleic acids that modulate HO-I activity, it fails to disclose which of the sequences sharing about 80% sequence identity to SEQ. ID No: 1 also having the biological activity of HO-I, thus the skilled artisan can not practice the invention without undue experimentation.

The prior rejection of claim 1-22 under 35 U.S.C. 112, first paragraph is withdraw in view of the newly submitted Exhibits 15, 16, and 18, indicating that the method have been extended to heart and kidney grafts since the filing the instant application; and in

view of Exhibits 11-14, and arguments that rodent models are generally considered as clinically relevant by the skilled artisan in organ transplantation art.

Claim Objections

Claim 15 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax numbers for the organization where this application or proceeding is assigned are 703-308-8724 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinsky, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
December 14, 2001

JAMES KETTER
PRIMARY EXAMINER